REMARKS

Claims 75, 76, 78, 80, 82, 83, 87-106, and 108-112 are pending and stand finally rejected in the Office Action dated March 31, 2009 ("the Action"). A Request for Continued Examination is being submitted along with this response to the Action. Claims 75, 76, 78, 80, 82, 83, 88-101, and 104-106 are amended herein. Support for the amendments can be found in the specification and claims as originally filed. See, e.g., page 4, lines 16-20 (formula II). Aside from the claim amendments described below, Claims 76, 80, 82, 83, and 92 are amended to correct typographical errors. No new matter is added by virtue of these amendments. Claim 87 has been cancelled. Claims 75, 76, 78, 80, 82, 83, 88-106, and 108-112 are therefore pending, reconsideration of which is requested in view of the following remarks.

The Rejection under 35 U.S.C. § 112, First Paragraph

Written Description

Amendments to the Claims

It is the position of the Examiner that the amendments to Claims 75, 78, and 82 submitted in the communication filed by applicants on January 15, 2009, introduced new matter into the claims. In the view of the Examiner, there is no support in the specification as originally filed for the claim amendment that R_7 in formula (I) can be hydrogen when X_2 is NR_4. Applicants disagree. Support for the amendment can be found, for example, at page 32, Example 1, and pages 33-37, compounds **2-27**. While not acquiescing with the Examiner's position, but in order to facilitate prosecution, Claims 75, 78, and 82 have been amended and now recite formula (II). Support for formula (II) can be found in the specification at, e.g., page 4, lines 16-20. Applicants respectfully request withdrawal of the rejection.

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Amendments to the Specification

It is the position of the Examiner that the amendments to the specification submitted in the communication filed on January 15, 2009, introduced new matter into the disclosure. Applicants disagree. However, while not acquiescing with the Examiner's position, but in order to facilitate prosecution, applicants have canceled the previously submitted specification amendment, "R_7 is hydrogen," at page 4, line 14, and at page 7. The grounds for the rejection are now moot and applicants request withdrawal of the rejection.

Enablement

The Examiner has rejected Claims 75, 76, 78, 80, 82, 83, 87-106, and 108-112 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner acknowledges that the specification is enabling for a method of inhibiting Raf kinase activity in a human or animal subject suffering from a Ras/mitogen-activated protein kinase signal pathway-mediated cancer disorder selected from the group consisting of melanoma, breast cancer, prostate cancer, lung cancer, pancreatic cancer, thyroid cancer, bladder cancer, colon cancer, liver cancer, myeloid leukemia, and villous colon adenoma, comprising administering to the human or animal subject a composition comprising an amount of a compound of the formula (I). However, in the view of the Examiner, the specification does not reasonably provide enablement for inhibiting Raf kinase activity in a human or animal subject comprising administering a composition comprising **any compound** represented by formula (I). It is the position of the Examiner that the specification fails to provide information that would allow the skilled artisan to practice the invention without undue experimentation. Applicants respectfully disagree for the reasons set forth below.

As an initial matter, applicants note that the claims, as amended, are now directed to compounds encompassed by formula (II). Accordingly, the Examiner's comments regarding compounds encompassed by formula (I) in which R_7 is loweralkyl are moot. Furthermore, more than one thousand compounds described in the specification fall within the scope of formula (II).

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Undue Experimentation Is Not Required to Understand the Scope of the Claimed Compounds

It is the position of the Examiner that the specification does not provide guidance as to what compounds have activity, and one would need to know the activity profile of the specific compounds tested in order to understand the scope and breadth of the claims. Applicants disagree. Experimentation to determine compounds that fall within the scope of the claimed genus is routine. The specification teaches that a Raf inhibitor is a compound that exhibits an IC_{50} with respect to Raf kinase activity of no more than about 100 μM, and more typically not more than about 50 μM. (See specification, page 10, lines 6-8.) The level of Raf kinase inhibitory activity, *per se*, of an individual compound is irrelevant, provided the compound meets the criterion as defined in the specification of exhibiting an IC_{50} with respect to Raf kinase inhibitory activity of no more than about 100 μM. Any compound within the scope of formula (II) that exhibits an IC_{50} with respect to Raf kinase activity of no more than about 100 μM could be used to practice the claimed method.

As pointed out in Example J of the United States Patent and Trademark Office Training Materials for Examining Patent Applications With Respect to 35 U.S.C. Section 112, First Paragraph - Enablement of Chemical/Biotechnical Applications (the "Training Materials"), a genus claim is enabled throughout its scope if the experimentation needed to determine the operative embodiments would not be undue. It is within the skill of the art to determine the Raf kinase inhibitory activity of a compound, and the specification provides two assays that can be used to measure Raf kinase inhibitory activity. (See specification, pages 307-309, Examples 1401 and 1402.) Accordingly, determining the operative embodiments of the invention, i.e., which compounds within the claimed genus exhibit sufficient Raf kinase inhibitory activity to be used in the claimed method, would not require undue experimentation.

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Structural Variation Among the Claimed Compounds Is Not Fatal to Enablement

The Examiner further comments that the compounds of the invention have different functional groups and therefore will have different properties and different Raf kinase inhibitory activity. Based on this contention, the Examiner then concludes the following: "Thus, the instant claimed invention as discussed is **highly unpredictable**." Action, page 10 (emphasis in original). Applicants disagree with this reasoning. Although the level of Raf kinase inhibitory activity may vary from compound to compound, as discussed *supra*, the specific level is irrelevant, provided the level of inhibitory activity is no more than about 100 μM. Applicants point out that, unlike Example J of the Training Materials, which only disclosed nine compounds, some of which were inoperative, all of the more than one thousand compounds of the claimed invention tested, having different functional groups, showed a Raf kinase inhibitory activity at an IC_{50} of less than 5 μM. Therefore, not only are all of the tested compounds Raf inhibitors, as defined in the specification, but all of the compounds tested demonstrated activity well within the scope of this defined term.

Moreover, breadth of structural diversity does not necessarily equal unpredictability, and the Examiner has failed provide acceptable evidence or reasoning to support the contention that such diversity corresponds to unpredictability with respect to the claimed methods. See *Ex parte Cho*, Appeal No. 2001-2646 at page 9 (Bd. Pat. App. & Interf. 2003), citing *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971) ("It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning...."). As emphasized on page 8 of *Cho* in the context of an accusation regarding allegedly over-broad claims in that case, an "examiner must do more than point to a lack of evidence supporting the breadth of the claims. The burden is not on the applicants to show that the disclosure in the specification is correct; the burden is on the examiner to show that it is not." Here, the Examiner has failed to provide specific evidence or reasoning as to how activity

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differences among the compounds reasonably correspond to unpredictability and hence, non-enablement, with respect to the claimed methods. "Pointing out a lack of independent evidentiary support is not enough" to carry the burden of establishing a *prima facie* case of non-enablement. *Id.* at page 9.

An in vitro/in vivo Correlation Is Established and Is Indicative of Enablement

It is also the position of the Examiner that the specification provides no evidence that the compounds of the invention actually inhibit Raf kinase activity in a human or animal. There is no requirement that applicants provide evidence from human clinical trials. See M.P.E.P. § 2107.03 (IV). Indeed, with respect to the merits of *in vitro* data, the Court of Appeals for the Federal Circuit has stated:

> *In vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with respect to the particular pharmacological activity are generally predictive of *in vivo* test results, i.e., there is a reasonable correlation there-between. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

Cross v. Iizuka, 753 F.2d 1040, 1050 (Fed. Cir. 1985). Evidence from *in vitro* testing that shows a compound or compounds exhibit a particular biological activity will be sufficient to show a therapeutic use if the biological activity is reasonably correlated to the therapeutic use. See M.P.E.P. § 2107.03 (III). A reasonable correlation can be established by data documenting the activity of the compound(s), arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. See *id.* at § 2107.03 (I). Moreover, the enablement requirement is satisfied as long as at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim is disclosed. *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970).

As discussed *supra*, more than one thousand compounds of the claimed invention showed Raf kinase inhibitory activity in *in vitro* testing that satisfies the specification's definition of a "Raf inhibitor." The correlation between inhibition of Raf kinase inhibitory activity and the

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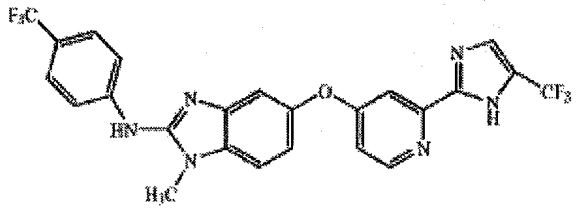
treatment of cancer was known in the art at the time of filing the application. See, e.g., Specification, page 2, line 30, to page 3, line 16. The burden is on the Examiner to provide reasons for a lack of correlation between an *in vitro* example and a therapeutic use. See M.P.E.P. § 2164.02. Applicants submit the Examiner has not provided any such reasoning to refute the correlation between the significant Raf kinase inhibitory activity demonstrated by the compounds of the invention and the therapeutic use of the compounds to treat the cancers listed in the claims. Indeed, the Examiner offers no evidence or reasoning specific to Raf kinase inhibition to counter assertions put forth in the present specification.

Evidence of structural similarities between a compound known to have a particular therapeutic use and the claimed compound(s) also may provide support of the asserted therapeutic use of the claimed compound(s). See M.P.E.P. § 2107.03 (II). An applicant may submit evidence after the filing of the application that demonstrates the claimed invention works. See *id.* at § 2164.05. Such evidence in regard to the instant application is provided, for example, in U.S. Patent No. 7,482,367 (the "'367 patent"), which discloses a Raf kinase inhibitor with substantially similar structural features to the claimed compounds. See column 43, Example 1 and Claim 1; see also columns 98-100, Example 82, which demonstrates the Raf kinase inhibitory activity of the compound of Example 1. The structure of the compound in Example 1 of the '367 patent is shown below:



The '367 patent provides *in vivo* data demonstrating that the compound of Example 1 caused significant tumor growth inhibition or tumor regression in mice xenograft models of melanoma, colorectal carcinoma, and leukemia tumors. See columns 103-107, Examples 84, 85, and 86, and column 107, Table 7. The *in vitro* data provided in the specification demonstrating

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that more than one thousand compounds of the claimed genus exhibit significant Raf kinase inhibitory activity, together with the *in vivo* data provided in the '367 patent demonstrating that a Raf kinase inhibitor with substantial structural similarity to the claimed genus was effective in inhibiting tumor growth in melanoma, colorectal carcinoma, and leukemia xenograft models, provides additional evidence that the claims are enabled throughout the scope of the genus of compounds recited in the present claims.

It is also the Examiner's position that there are no working examples comprising administering any compounds of formula (I) and that undue experimentation would be required to practice the claimed invention. Applicants presume this same contention would be applied by the Examiner to compounds of formula (II). Applicants disagree: undue experimentation is not determined solely on the basis of the quantity of experimentation or the time and expense involved. A considerable amount of experimentation is permissible if it is routine. See M.P.E.P. § 2164.06. Furthermore, working examples are not required to comply with the enablement requirement. See *id.* at § 2164.02. While drug development may be a challenging endeavor, the steps in the process, from *in vitro* testing and animal studies to studies in humans, are routine and within the skill of the art, and the specification provides guidance as to methods of administering the compounds of the invention, including dosages and routes of administration. (See specification, page 28, line 14, to page 30, line 10.) Accordingly, applicants submit it would not require undue experimentation to practice the claimed invention.

Summary and Conclusion

The burden is on the Examiner to provide evidence or technical reasoning to support a rejection for lack of enablement. See M.P.E.P. § 2164.04. Applicants submit the Examiner has not met that burden. The specification demonstrates that over one thousand compounds that fall within the scope of formula (II) exhibit Raf kinase inhibitory activity well within the specification's definition of this term; a correlation between Raf kinase inhibitory activity and the treatment of certain types of cancer was known in the art at the time of filing of the application,

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and the Examiner has not provided specific evidence or reasoning to counter this knowledge; the specification provides guidance as to dosing and methods of administration; and although drug development may be a lengthy process, selecting a compound and performing the required *in vitro* and *in vivo* testing, including conducting clinical trials, is routine and within the skill of the art. Furthermore, the specification provides methods of making more than one thousand compounds, provides assays for testing the compounds to determine Raf kinase inhibitory activity, and provides guidance as to how to use the compounds to treat a variety of cancers. Accordingly, the specification enables a person skilled in the art to make and use the invention. Applicants respectfully request withdrawal of the rejection.

CONCLUSION

Applicants believe that Claims 75, 76, 78, 80, 82, 83, 88-106, and 108-112 are in condition for allowance. Reconsideration and favorable action is requested. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1649.

Respectfully submitted,

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